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Ethnicity or environment: Effects of migration on ovarian reserve among Bangladeshi women in the UK

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Running title: Effects of environment on ovarian reserve

Capsule: Differences in ovarian reserve between age-matched Bangladeshis who moved to London as children or adults highlight the influence of developmental environments rather than ethnicity on the tempo of reproductive ageing.

Conflicts of interest: None declared.

Abstract

Objective: To assess whether the quality of early childhood environments among different groups of Bangladeshi women, including migrants to the UK, contributes to variation in ovarian reserve and the rate of reproductive ageing in later life.

Design: Cross-sectional study.

Setting: London (UK) and Sylhet town, NE Bangladesh.

Patients: 179 healthy women volunteers aged 35-59 divided into four groups: 1) 36 Bangladeshis living in Sylhet, Bangladesh; 2) 53 Bangladeshis who migrated to the UK as adults; 3) 40 Bangladeshis who migrated to the UK as children aged 0-16; and 4) a reference group of 50 women of European origin living in London.

Intervention: None.

Main Outcome Measures: Levels of serum anti-Müllerian hormone, inhibin B, follicle-stimulating hormone and estradiol, and anthropometrics derived from biomarkers; reproductive, demographic and health variables from structured questionnaires.

Results: Bangladeshi migrants who moved to the UK as children and European women had a highly significantly larger, age-related ovarian reserve compared to migrant Bangladeshis who had moved to the UK as adults or Bangladeshi women still living in Bangladesh. There were no other significant covariates in the model.

Conclusion: The study points to the importance of childhood development in considering variation in ovarian reserve across different ethnic groups. Clinical studies and research in assisted reproductive technologies (ART) have emphasized the role of genes or race in determining inter-population variation in ovarian reserve. Early life developmental factors should be given due consideration when evaluating inter-group differences in response to ART.

Key words: Ovarian reserve, migration, ethnicity, environment, Bangladeshis

Introduction

Identifying biomarkers of fecundity has become increasingly important in clinical settings as women postpone childbearing to later years and the incidence of assisted reproductive technologies (ART) rises among older women (1-4). Fertility centers routinely assess markers of ovarian reserve in women seeking treatments in an effort to predict who might benefit most from these technologies, although the value of such tests for predicting pregnancy outcome continues to be debated (1, 5-7). Success using ART in terms of implantation rates, miscarriages, and live pregnancies appear to vary among women from different ethnic groups (8-15). This variation is frequently described in the clinical literature as “racial” implying a primarily genetic underpinning for this variation (8, 16-20), although the term can also have other sociological meanings. The causes of this variation, however, are not fully understood and may include environmental factors such as differences in socioeconomic status, cultural variation in approaches to ART, differential prevalence of diseases such as polycystic ovarian syndrome, and variation in quality of care provided to different ethnic groups (21, 22).

Many aspects of ovarian function vary markedly across women of reproductive age in different populations. For example, inter-population variation has been documented for reproductive steroid hormone levels (23-25), reproductive protein hormone levels (27-28), miscarriage rates (29-30), menstrual cycle characteristics such as cycle length and days of menstrual bleeding (31-33), and the length of the reproductive lifespan measured by age at menarche (34), and menopause (35). Inter-population variation in rates of reproductive aging and age at menopause could explain why age-matched women from different ethnic groups vary in hormonal levels reflecting ovarian reserve, and why they respond differently to ART (8, 20, 36). Rather than offering primarily genetic explanations, reproductive ecologists have focused instead on aspects of the environment such as nutritional stress,

excessive energy expenditure, or immunological challenges to explain the often significant differences in gonadal function across populations (37-39), although the role of genetics has not been overlooked (40). More recently, effects of the developmental environment on adult ovarian function have also been assessed (41-43). In our earlier work, for example, we found significant differences in levels of reproductive steroids, length of the reproductive lifespan, and rates of ovulation among age- and socio-economically matched Bangladeshi women depending on whether they had grown up in Bangladesh or the UK (32, 41-43).

Ovarian reserve has been calculated in women using biomarkers such as anti-Müllerian hormone (AMH), inhibin B, follicle-stimulating hormone (FSH) and more directly by antral follicle count (AFC) using ultrasonography. Some studies have also included assessments of estradiol (E2) (44-47). Among these methods, both AFC (49-50) and AMH (7, 51-56) are generally considered the best predictors of ovarian reserve and outcome for ART, although AMH is a better measure of the quantity rather than quality of remaining oocytes in the ovary (5, 57). However, using several of these biomarkers together represents a more powerful approach than reliance on one or two methods (58-59).

The purpose of this paper is to evaluate effects of the environment and/or ethnicity on ovarian reserve among different groups of migrant Bangladeshi women aged 35-59 living in London who moved to the UK either during childhood (prior to menarche) or as adults. We compare these data to Bangladeshi women of the same ages still living in their home country who were matched against the migrants for place of origin and socioeconomic status, and to a reference group of British women aged 35-59 also living in London and of European descent. Ovarian reserve was assessed through measurement of serum levels of AMH, inhibin B, FSH and E2. Our goal was to examine potential differences in markers of

ovarian reserve across these groups that might reflect ethnicity or the environment to which they were exposed across the life course.

Materials and Methods

Study Participants

Blood was drawn from 207 women participating in a larger study (total n=540) of reproductive aging and related symptoms at midlife in London and Bangladesh that was conducted between September 2006 and August 2010 (60-61). The 207 women represented a convenience sub-sample of women who were willing to undergo phlebotomy which was conducted after women had completed questionnaires and anthropometry. Women were recruited from four different groups: 1) Bangladeshi women still resident in their home country and living in Sylhet in the northeast part of the country from where the majority of UK migrants originate (sedentees, n = 36); 2) Bangladeshi women who migrated from Sylhet to the UK as reproductively-aged adults, considered as older than age 16 which is the oldest recorded age at menarche (adult migrants, n = 53). Women had spent a minimum of two years in the UK; 3) Bangladeshi women who had migrated to the UK from Sylhet prior to the age of menarche (child migrants, n = 40); and 4) women of European origin and living in London (Europeans, n = 50). Given the relatively recent history of migration of Bangladeshis to the UK, we were unable to recruit child migrants aged 50-59; women from this age-group are therefore missing in some analyses.

Eligibility criteria included being aged 35-59, no history of hysterectomy or oophorectomy, no current pregnancy, lactation or use of hormonal contraceptive within the past six months, and no thyroid condition or infertility that might affect reproductive hormone levels. After excluding samples that came from women with self-reported diabetes, and polycystic ovarian syndrome, and some second-

generation women who were too small a group to be compared statistically, 179 women remained for analyses.

In Bangladesh, women were mostly recruited through personal contacts and the use of snowball techniques where initial recruits refer other potential subjects to the project (62), while in London the migrants were recruited primarily through community centers and also snowball techniques. Women of European origin were primarily recruited from advertisements in local newspapers. Women were financially compensated for their time and effort.

Ethical approval

Ethical approval was obtained from the Ethics Committees at University College London, Durham University, M.A.G. Osmani Medical College, Sylhet, Bangladesh and the Institutional Review Board at the University of Massachusetts, Amherst. All women received an information sheet about the study written in either English or Bangla, and provided a signed consent form prior to participation. Data were stored in accordance with the Data Protection Act (UK).

Questionnaires

All women completed a standardized, structured questionnaire requesting demographic details, information on reproductive and developmental history, educational and employment history, as well as migration and health histories. The questionnaires were translated first into Bangla by native speakers and then back-translated into English to check for inaccuracies, and were administered to participants in either Bangla or English as appropriate by trained researchers. They were also piloted in both languages prior to the study.

Since older Bangladeshi women were usually born at home prior to the routine collection of birth records in Bangladesh, we compiled an event calendar which was used to assist in age reconstructions. This incorporated memorable occasions in Bangladesh such as the War of Independence, Victory Day, the India-Pakistan War of 1965, and major national disasters such as cyclones. Ten percent of Bangladeshi women did not know their exact age and the majority of these were sedentees (50% of this group); only 2% of the Bangladeshi adult migrants and none in the other two groups fell into this category. For the recollection of last menstrual period for older, post-menopausal women, we asked them to remember the season of the year, or any family, political or national event that occurred at that time. Event history calendars are frequently used in survey methodologies to assist in reconstructing past events of interest which may not be otherwise documented exactly (63).

Anthropometry

Height, weight, arm circumference, triceps skinfold, waist and hip circumference were measured using standardized techniques (64). The Body Mass Index (BMI) was calculated from the height and weight measurements as $\text{weight (kg) / height (m}^2\text{)}$, and waist-to-hip ratio (WHR) was calculated from waist and hip circumferences as waist/hip (cm) .

Serum samples

One 5 ml blood sample was collected from each woman by venipuncture from the antecubital vein on days 4-6 of the menstrual cycle for pre-menopausal women and at any time for post-menopausal women. Each sample was centrifuged as soon as possible after collection to separate the serum and was then stored at -20°C either at the laboratory for the Centre of Reproductive Science at University College London (UCL), or at the Microbiology Laboratory of the M.A.G. Osmani Medical College, Sylhet, Bangladesh. Samples from the latter were transported by air to the UK on dry ice prior to assay at UCL.

Serum inhibin B levels were assayed using an enzyme-linked immunosorbent assay (ELISA) kit (Diagnostic System Laboratories, Texas, USA). The minimum detection range for this assay is 10 pg/ml. The mean intra- and inter-assay CVs are 6.2 and 7.2% respectively. Serum AMH was assayed using an ELISA kit (Immunotech SAS, Marseille, France) with a sensitivity of 0.42 pmol/L. Inter- and intra-assay variation were <15% using an in-house quality control. Serum FSH levels were analysed using an electrochemiluminescence immunoassay kit manufactured by Roche Molecular Biochemicals, Mannheim, Germany. The detection range of this assay varies between 0.10 mIU/L and 200 mIU/L. Mean intra and inter-assay CV are 10%. Serum E2 levels were also analysed using an electrochemiluminescence immunoassay kit by Roche Molecular, Biochemicals, Mannheim, Germany. Mean intra and inter assay CV are < 10%. The measuring range of this assay varies between 5 pg/mL and 4300 pg/mL.

Statistical Analyses

Women were divided into age quintiles (35-39, 40-44, etc) to compare more effectively when the different groups (sedentees, adult migrants, child migrants and Europeans) began to experience changes in the hormonal markers of ovarian reserve that might signal the menopausal transition. Menopausal status was categorized using WHO criteria where women were considered premenopausal if they had menstruated within the past two months, peri-menopausal if they had menstruated within the past 3-12 months, and post-menopausal if they had not experienced menses within the past 12 months (65). Very few women reported being peri-menopausal. For the analyses below, therefore, pre- and peri-menopausal women were combined so that all women who had menstruated within the past 12 months were considered to be pre-menopausal. Median ages at menopause were computed by probit analysis. BMI was included as a covariate in multivariate regressions since it can affect measurements of various reproductive hormones (66-70) and differed significantly between groups in our earlier studies (71).

Religion (Muslim/Hindu) was included as a variable because Hindu women formed part of the sample in Sylhet. The latter tended to be poorer, thinner and have heavier workloads than Muslim women and these factors could confound the data. Infectious disease burden was previously a significant predictor of menopausal age among the larger study of reproductive ageing among women (60). It was calculated by adding together the number of childhood and other infectious diseases each participant reported as ever experiencing in the past on a yes/no basis when presented with a list of possible illnesses. These included chicken pox, mumps, whooping cough, diphtheria, tuberculosis, paratyphoid, hepatitis, diarrhea and pneumonia, and were coded as 0-2, 3-4, and 5-6 exposures. Intestinal parasite exposure included intestinal worms (helminths) and microbial parasites, and was categorized as yes/no.

Data for continuous variables were not distributed normally across groups necessitating the use of non-parametric statistics. We used Kruskal-Wallis analysis of variance to analyze differences between groups for anthropometric variables (height, weight, triceps skinfold thickness, waist and hip circumferences, BMI and WHR), plus parity and recalled mean age at menarche. Chi-square analysis was used to compare differences between groups for categorical variables. Because of missing data, the sample size for the variables may differ slightly in the analyses.

Data for all the hormones were log-transformed prior to multivariate analyses. A non-linear exponential regression model was used to explore differences in the menopausal transition between groups.

Multivariate regression was used to test for differences in ovarian reserve between groups using all four hormones together from each individual, and controlling for age, menopausal status, religion, BMI, exposure to infectious diseases and exposure to intestinal parasites. Including all of the hormones from each single individual in one model provides more power than a univariate analysis. Separate general linear models for each individual hormone and controlling for the same covariates were also run to test

for significant differences in ovarian reserve between groups. In addition, general linear models were run to examine whether there were any differences in hormone levels between adult Bangladeshi migrant women based on the length of time they had spent in the UK since immigrating (coded as ≤ 15 years or >15 years), and whether there were differences in hormone levels among child migrants depending on the age at which they had immigrated as children (0-8 and 9-16). Significance was determined using a p-value of <0.05 . Data were analysed using SPSS v.20, and Systat 12.

Results

Sample characteristics

We first compared differences between the sub-sample ($n=207$) of women under scrutiny here who contributed blood samples, and the larger sample ($n=540$) from which they were drawn. There were no significant differences between the sub-sample and main sample in age distributions, reported ages at menarche or menopause, or the distribution of women across menopausal status (pre- versus post-menopausal). Comparisons were repeated for each of the four different groups under consideration (sedentees, adult migrants, child migrants and Europeans) between the sub-sample and main sample (72). There was a significantly greater number of Hindus among the sedentees (36%) in the sub-sample compared to the main group (22%, $p<0.05$). There was also a significant difference in BMI between the sedentees in the sub-sample here compared to sedentees in the main group of women (independent t-test: $t_{68.73}= 2.304$; $p<0.05$); sedentees in the sub-sample were thinner overall. In addition, sedentees in the sub-sample had a lower perceived financial status ($\chi^2=19.06$ $df=3$, $p<0.001$), suggesting that Hindu women, despite being middle class, were generally less well-off (72).

Descriptive statistics for the participants in the sub-sample under scrutiny in this paper are presented in Table 1. The mean age of the child migrants *was* significantly lower as a result of the historical pattern

of migration of Bangladeshis such that older women aged 50+ are not yet well represented in the UK. All of the anthropometric indices except for hip circumferences were significantly different between the Europeans and Bangladeshis. The European women were significantly taller ($H = 56.193$, $df = 3$, $n = 179$, $p < 0.001$), had a significantly smaller waist circumference ($H = 13.63$, $df = 3$, $n = 177$, $p = 0.003$), and a significantly smaller WHR ($H = 23.62$, $df = 3$, $n = 177$, $p < 0.001$). None of the Bangladeshi groups, however, differed significantly from each other in these characteristics, but both the sedentees and European women had a significantly ($p < 0.05$) lower BMI compared to either the child or adult migrants. European women also reported having fewer children than Bangladeshis. Similar to our earlier work with a younger group of women, child migrants recalled an earlier age at menarche even than the Europeans (41). Median ages at menopause differed between groups, and compare well with median ages computed in the larger sample of women ($n=485$) who did not participate in the study of hormonal levels presented here (60).

The menopausal transition

Compared to both Bangladeshi sedentees and adult migrants, a higher proportion of European women remained premenopausal at older ages and, consequently, reached the menopause later than the Bangladeshi groups. Median age at menopause was significantly different across groups, with women still living in Bangladesh and adult migrants having reached the menopause earlier than European women or women of Bangladeshi origin who had grown up in the UK (Table 1). In support of this picture of an earlier age at menopause, levels of AMH and inhibin B had reached the limits of assay detectability by age quintile 45-49 among sedentees and adult migrants, whereas European women still had detectable levels ten years later at 55-59 (Figure 1 and Table 1, Supplementary Materials). Similarly, levels of FSH had already begun to rise in both sedentees and adult migrants among women aged 40-44

and were twice as high as women of European origin and child migrants from the ages of 40-44 onwards. It is not until the age groups of 54-59 that levels of FSH were comparable across groups (Table 1, Supplementary Materials).

A non-linear, exponential model was used to explore levels of AMH, inhibin B and FSH as a function of age across the menopausal transition (Table 2, Supplementary Materials). There was a significant difference between Bangladeshi sedentees and European women in the rate of decline of levels of AMH and inhibin B and the rate of increase in levels of FSH, but not between sedentees and adult migrants. In other words, the two latter Bangladeshi groups who spent their childhoods in Bangladesh had similar age-related hormonal trajectories as they approached the menopause. European women appeared to have higher levels of AMH and inhibin B during younger age-quartiles, and reached non-detectable levels of these hormones at older ages compared to Bangladeshi sedentees and adult migrants (Figure 1 and Table 1, Supplementary Materials).

Hormone Levels

Mean levels of serum inhibin B, AMH, FSH and E2 by age quintiles across the four groups of women are shown in Figure 1 and Table 1 in Supplementary Materials. We ran a multivariate regression to compare ovarian reserve across the four groups of women that included all of the serum hormones, and controlling for age, BMI, recalled infectious disease and parasite loads, recalled age at menarche, menopausal status, parity and religion. Child migrants ($F_{4,142} = 3.814$, $p < 0.01$) and women of European descent ($F_{4,142} = 3.315$, $p < 0.05$) had a highly significantly, age-related, larger ovarian reserve indicated by their respective serum hormone levels compared to Bangladeshi sedentees and adult migrants (Table 2). Age and menopausal status were significant predictors of hormone levels but none of the other variables was significant. When each hormone was regressed separately, only child migrants (and not adult migrants or women of European origin) differed significantly from sedentees, but not for FSH

(Table 3). Parity was a significant predictor in these regressions for inhibin B, AMH and E2 but not for FSH. Length of time spent in the UK as an adult migrant had no significant effect on any of the hormone levels (estimate of mean difference \pm SE: inhibin B=3.2647 \pm 0.25; AMH=0.9302 \pm 0.48; FSH=2.9718 \pm 0.32; E2=3.5445 \pm 0.22; $p>0.05$). Unlike our earlier study of salivary progesterone levels (42), we found no significant differences in any of the serum hormone levels between child migrants who came to the UK between ages 0-8 and those who arrived later at ages 9-16 (estimate of mean difference \pm SE: inhibin B=3.2254 \pm 0.88; AMH=1.6995 \pm 1.14; FSH=2.1796 \pm 0.47; E2=3.2857 \pm 0.66; $p>0.05$).

DISCUSSION

Our research targeted three different groups of Bangladeshi women aged 35-59, matched for socioeconomic status, who were either born and grew up in Bangladesh (sedentees and adult migrants), or who were born in Bangladesh and grew up in the UK (child migrants). Despite having the same ethnic and geographic origins (Sylhet, NE Bangladesh), child migrants differ significantly in their biomarkers of ovarian reserve as they approach the menopause. Women who developed as children in the UK (up to age 16) have a significantly greater, age-matched, ovarian reserve -- marked by higher levels of AMH and inhibin B, and significantly lower levels of FSH -- compared to Bangladeshi women who either remained in Sylhet or who moved to the UK as adults. The observed differences are not a function of time spent in the UK since, for adult migrants, there is no association between time since migration and levels of hormones indicating ovarian reserve. The results presented here are consistent with our earlier findings among younger Bangladeshi women aged 18-35, where child migrants and second-generation British-Bangladeshis had significantly higher levels of salivary progesterone, rates of ovulation and an earlier recalled age at menarche compared to either adult migrants or sedentees in Bangladesh, and were more similar to a reference group of European women aged 18-35 (41-43).

Bangladesh ranks as one of the poorest countries in the world with a Gross National Income (GNI, nominal, Atlas Method) of US \$1,080 compared to a GNI of US \$42,690 for the UK (73). In 2010, almost half (43%) of the Bangladeshi population was living below the international income poverty line of US \$1.25/day (73). Frequent floods with consequent deleterious sanitation conditions in Bangladesh lead to high levels of infectious diseases, while health care is inferior to countries like the UK (60). Life expectancy in Bangladesh in 2015 remains low relative to the UK: 69 versus 78 years for males, and 73 versus 83 years for females (74). However, the Bangladeshi migrants that participated in our studies are from relatively affluent, well-fed families who own land in Bangladesh, can afford servants, and have the means to migrate. Neither nutritional stress nor high outputs of energy can therefore explain the differences we document between those who live in Bangladesh compared to the UK. The mean BMI of sedentees is, in fact, above the WHO threshold for overweight and comparable to the similarly slightly overweight European women. Both adult and child migrants are fatter than either the sedentees or Europeans, suggesting they put on weight once they live in the UK. The diet of first-generation Bangladeshi migrants remains faithful to the cultural norms of their home country facilitated by the availability of South Asian foods in London including many imported items such as frozen river fish from Sylhet (75). However, meat and chicken are much cheaper in the UK compared to Bangladesh and are eaten in greater quantities, while the consumption of fruit and vegetables declines significantly (76).

A life history approach is used frequently in studies of reproductive ecology whether applied to humans (77- 79) or other species (80-81) and posits, based on substantial evidence, that trade-offs exist between growth, reproduction and maintenance of organisms (82-83). Using this approach, we suggest that the more challenging environment that individuals meet while growing up in Bangladesh compromises their reproductive development. Such a trade-off would lead to an adult phenotype with lower reproductive capacity compared to individuals who grow up in the UK. This hypothesis is supported by the regression

analysis in this paper that found significant differences in hormone levels and *the trajectory* of reproductive aging between women who grew up in Bangladesh versus the UK, while controlling for numerous covariates that might affect reproductive hormone levels. In an earlier paper, we found that infectious disease load was a significant predictor of age at menopause among a larger sample of Bangladeshi women, but this variable was not significant in the analyses here of a smaller group of women sampled for hormone levels (60). We have similarly suggested, however, in past papers that life history trade-offs could explain differences in other reproductive and developmental parameters between Bangladeshis who grow up in contrasting UK and Bangladeshi environments, including ages at adrenarche and menarche, levels of salivary progesterone and rates of ovulation (41-43, 84).

The study presented here assessed ovarian reserve using four hormonal biomarkers commonly used in clinical and research settings. We could not use AFC as an additional measure due to the invasive nature of this procedure for normal, healthy volunteers, as well as the additional expense that this would have entailed. The study is limited in being cross-sectional and having a relatively small sample size in each group due to the intensive nature of the work involved and the demands made of healthy participants. Due to the migration history of Bangladeshis, we were unable to recruit child migrants aged 50-59, meaning that there was only one woman who had reached the menopause from this group. Child migrants are therefore missing from some analyses among older women. Our recruitment methods were not random as it is virtually impossible to recruit among the UK Bangladeshi migrant population using such techniques, so we relied primarily on local contacts and snowballing strategies. This may have introduced some unintentional biases among the samples. The sedentees also included a large proportion (36%) of Hindus who follow a somewhat different diet and lifestyle than Muslims in Sylhet, have a lower socioeconomic status, and were more likely to volunteer for phlebotomy, possibly because of the greater remuneration involved for giving blood but, perhaps, also because Muslim women were

required to ask for permission from their husbands to participate in the study which introduced additional complications for their inclusion (72). However, both Hindus and Muslims in Sylhet are Bengali in ethnic origin (85). The study did not collect any data that were designed specifically for analyses of genes linked to ovarian reserve or the menopause, nor did we have ethical permission to do so.

This study cannot address potential mechanisms that might explain why ovarian reserve should differ significantly between child migrants, adult migrants and Bangladeshi sedentees. Ovarian ageing and menopause is determined by the initial number of follicles with which women are endowed *in utero* together with rate of loss from atresia and the rate at which follicles are recruited in each menstrual cycle across the reproductive life-span (35), although recent studies suggest women may have the ability to replenish their stock of oocytes early in life (86-89). Prior autopsy studies have pointed to significant inter-population variation in the uterine endowment of follicles (90-94), implying that genes and the fetal environment together determine inter-individual variation in this characteristic, but this would not explain why Bangladeshi women who migrated during childhood (and presumably experienced similar environments during fetal life) would differ significantly in ovarian function as adults. To explain variation in ovarian reserve with age, either the rate at which follicles are recruited differs across the life course and in individual cycles, or the rate of follicular loss differs through the process of atresia. These mechanisms cannot be measured from our data, but the lower levels of AMH documented for sedentees and adult migrants imply a higher rate of follicle recruitment and a faster exhaustion of the follicular pool among these groups of women (52, 95-97). It is possible that the rate of recruitment might somehow be “set” in childhood during a critical period. Alternatively, there may be other processes involved in ovarian growth and maturation that we do not yet fully understand that might be affected by environmental changes in early life. Anderson et al. for example, have recently compared follicles obtained from biopsy specimens from a small number of prepubertal, pubertal and adult

ovaries, and concluded from a histological study of these samples that ovarian maturation continues across childhood and puberty, resulting in full adult “competence” perhaps only in the mid-20s (98). This would coincide with demographic observations of women’s peak fecundity in natural fertility populations (99). Further comparative studies of this kind are needed.

Conclusions

The study here points to the importance of the developmental environment during childhood rather than ethnicity in influencing ovarian reserve. There is no *a priori* reason to believe that the separate groups of Bangladeshi women should differ significantly in their genetic characteristics. All of the sedentees and migrants are of Bengali origin, and come from the same geographic area (Sylhet in NE Bangladesh) from where the majority of UK Bangladeshis emigrate (100), and generally share a similar socioeconomic history (101-102). The migrants constitute a multi-generational population that allows for the recruitment of individuals who entered the UK at different stages of the life course.

Intermarriage with other ethnic groups also remains rare (103). Studies that purport to isolate genetic characteristics in relation to menopause rarely also manipulate the environment, but migration studies provide an excellent natural experiment in environmental change while holding genetic aspects constant (104-105).

In contrast to our findings, a number of papers describe differences in biomarkers of ovarian reserve between ethnic groups as “racial” (among “African Americans”, “Hispanics/Latinos”, “Asians” and “Whites”) (8-9, 14-15, 20, 36, 106). These and other studies suggest that establishing the genetic profiles of such ethnic groups will enable future predictions concerning the reproductive potential and physical health of women from these populations (1, 17, 107). Our research, however, shows that

Bangladeshi women from the same genetic background can vary as much among themselves *depending on their environment of development* as they can from women of a presumably different genetic origin (Europeans). It is therefore possible that variation observed in other ethnic groups is also a product of how developmental factors act to control the expression of genes. These distinctions have important policy implications for clinical settings and the application of ART and should be considered further by clinicians when evaluating the reproductive potential of women with age-related infertility issues.

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Authors' Roles

GB and KB interpreted the data, drafted the manuscript and analyzed some of the data. GB, SM, and LS designed the study, directed implementation, and data collection. KB, LM, LS, and TS collected the data. SM directed hormonal analyses, and assisted with data interpretation. AK analysed the data statistically and provided critical comments. RG and KB conducted the hormonal analyses. SM and LS edited the manuscript for intellectual content and provided critical commentary. OC provided logistical and laboratory support in Sylhet, Bangladesh. OC, LM, and TS provided critical comments on the manuscript.

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Conflict of Interest

None declared.

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Figure Captions

Figure 1: Mean serum reproductive hormone levels reflecting ovarian reserve across age quintiles by group. Levels shown without error bars for clarity of viewing. 10 pg/ml is the limit of detectability for inhibin B. Child migrants are not represented at older ages (50+).

Supplementary Figure Captions

Figure 1: Analysis of hormones as function of age using a non-linear exponential model to estimate the decline rate of hormonal level for AMH and Inhibin as the women get older. For FSH, it estimates the increasing rate of the hormone as women age. Scatter points represent the observed hormonal level while the lines represent the predicted value of the hormones as functions of age. Child migrant are excluded from the analysis due to lack of women >50 in the study.

Table 1. Descriptive variables for Bangladeshi and European women

Mean \pm SD	Sedentees	Adult Migrants	Child Migrants	Europeans
Sample size	36	53	40	50
Age ¹	46.6 \pm 7.39	45.52 \pm 6.61	39.57 \pm 3.7	47.14 \pm 7.09
Total number of children ²	2.97 \pm 1.5	3.52 \pm 1.64	3.42 \pm 1.22	1.0 \pm 1.27
Height (cm) ³	151.02 \pm 5.94	153.36 \pm 7.18	153.86 \pm 6.28	162.34 \pm 6.07
Weight (kg) ⁴	57.48 \pm 11.95	64.03 \pm 10.41	65.93 \pm 11.32	66.5 \pm 14.1
Body mass index (BMI) ⁵	25.15 \pm 4.78	27.14 \pm 3.41	27.68 \pm 4.15	25.18 \pm 4.97
Triceps skinfold (mm) ⁶	24.34 \pm 8.76	28.9 \pm 6.58	30.17 \pm 7.05	19.92 \pm 6.39
Waist circumference (cm) ⁷	84.08 \pm 11.07	87.37 \pm 9.71	85.42 \pm 9.29	79.51 \pm 11.86
Hip circumference (cm)	100.43 \pm 9.02	102.67 \pm 7.98	102.89 \pm 9.66	102.22 \pm 12.98
Waist-hip ratio ⁷	0.84	0.85	0.83	0.77
Infectious disease episodes (%)				
0-2	17	27	26	17
3-4	14	22	10	28
5-6	5	4	4	5
Recalled age at menarche ⁸	13.36 \pm 1.47	13.31 \pm 1.26	12.5 \pm 1.26	12.85 \pm 1.62
Mean age at menopause ⁹	46.32 \pm 3.76	47.09 \pm 4.4		49.97 \pm 4.66
Median age at menopause ¹⁰	46.89	49.94		52.59

¹ Child migrants are significantly younger compared to the other groups since older women could not be recruited (p<0.001)

² European women have significantly fewer children compared to the other groups (p<0.001).

³ European women are significantly taller than the other groups (p<0.001).

⁴ Sedentees weigh significantly less than the other groups (p<0.05).

⁵ Both sedentees and Europeans have a significantly lower BMI compared to the adult and child migrants (p<0.05).

⁶ Sedentees have significantly smaller triceps skinfolds compared to both migrant Bangladeshi groups (p<0.01), and Europeans have significantly lower skinfolds than the other groups (p<0.01).

⁷ Europeans have a significantly lower waist circumference and WHR compared to the other groups (p<0.01).

⁸ Child migrants have a significantly earlier recalled age at menarche compared to the other groups (p<0.01).

⁹ Recalled for post-menopausal women only, n=18 for sedentees, n=16 for adult migrants, and n=14 for women of European origin. There are only 2 post-menopausal women in the child migrant group.

¹⁰ Computed by probit analysis Fieller Bounds for Sedentees=43.78-49.57; for Adult Migrants=47.73-52.57; and for Europeans=49.12-60.75. Median menopausal age for each group is significantly different (p<0.05) from the others.

Table 2 Multivariate regression of log(AMH), log(inhibin B), log(FSH) and log(E2) comparing ovarian reserve between Bangladeshi sedentees, migrants and European women controlling for potential confounders.

	Roy's Statistic	Approx F	Num DF	Den DF	P-value
Intercept	150.978	5359.719	4	142	<0.001
Age	3.7235	132.1854	4	142	<0.001
Body mass index	0.0412	1.4627	4	142	0.2167
Infectious disease episodes*	0.0416	1.4858	4	143	0.2096
Menarche	0.0253	0.8993	4	142	0.4662
Menopausal status†					
post-menopausal	0.412	14.6251	4	142	<0.001
peri-menopausal	0.3291	11.6817	4	142	<0.001
Number of children	0.0586	2.0797	4	142	0.0866
Parasite load	0.0102	0.361	4	142	0.836
Religion‡	0.0214	0.7637	4	143	0.5506
Study groups¥					
adult migrants	0.0284	1.0074	4	142	0.4058
child migrants	0.1074	3.8137	4	142	0.0056
European women	0.0934	3.3154	4	142	0.0125

*Reference: 0-2 episodes †Reference: Pre-menopausal ‡Reference: Hindu ¥Reference: Bangladeshi sedentees

Table 3 Multivariate regression analyzing log hormone levels separately between groups and controlling for covariates.

Variable	Log(inhibin)			Log(AMH)			Log(FSH)			Log(E2)		
	Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	5.9337	0.8391	<0.001	6.5564	1.2024	<0.001	0.2145	0.659	0.7453	5.3321	0.8592	<0.001
Age	-0.0556	0.0151	<0.001	-0.1367	0.0217	<0.001	0.0409	0.0119	<0.001	-0.013	0.0155	0.4022
Body mass index	-0.0183	0.0128	0.1549	0.0126	0.0183	0.492	0.0055	0.01	0.5831	-0.0173	0.0131	0.1887
Infectious disease episodes*												
2-3	0.0595	0.1189	0.6173	-0.0672	0.1703	0.694	0.2182	0.0933	0.0208	0.0057	0.1217	0.9624
4-6	0.3732	0.1973	0.0605	0.3095	0.2827	0.2754	0.0795	0.1549	0.6087	-0.0407	0.202	0.8407
Menarche	0.0116	0.0385	0.7648	0.0031	0.0552	0.9551	0.0245	0.0303	0.4198	0.0238	0.0395	0.5473
Menopausal status†												
post-menopausal	-0.408	0.2208	0.0666	-0.6962	0.3164	0.0294	1.5478	0.1734	<0.001	-1.1785	0.2261	<0.001
peri-menopausal	-0.3488	0.268	0.1951	-1.0638	0.3841	0.0063	1.4359	0.2105	<0.001	-0.5292	0.2744	0.0558
Number of children	0.428	0.1993	0.0332	0.8096	0.2845	0.005	-0.1853	0.158	0.2425	-0.5939	0.1922	0.0023
Parasite load	0.1294	0.4976	0.7952	0.0803	0.7103	0.9101	0.3242	0.3944	0.4124	-0.3694	0.4798	0.4425
Religion‡												
Muslim	0.0521	0.2549	0.8384	-0.2186	0.3653	0.5505	0.0602	0.2002	0.7641	-0.2255	0.2611	0.3891
Other	0.0308	0.5341	0.9541	0.347	0.7654	0.651	-0.5791	0.4195	0.1695	-0.2182	0.5469	0.6905
Study groups¥												
adult migrants	0.1984	0.1752	0.2594	0.1126	0.2511	0.6545	-0.0272	0.1376	0.8437	-0.2049	0.1794	0.2554
child migrants	0.3915	0.2045	0.0576	0.6384	0.2931	0.031	-0.143	0.1607	0.375	-0.5958	0.2095	0.0051
European women	0.2011	0.501	0.6887	0.1266	0.718	0.8603	0.2753	0.3935	0.4853	-0.481	0.513	0.3501

*Reference: 0-2 episodes

†Reference: Pre-menopausal

‡Reference: Hindu

¥Reference: Bangladeshi sedentees

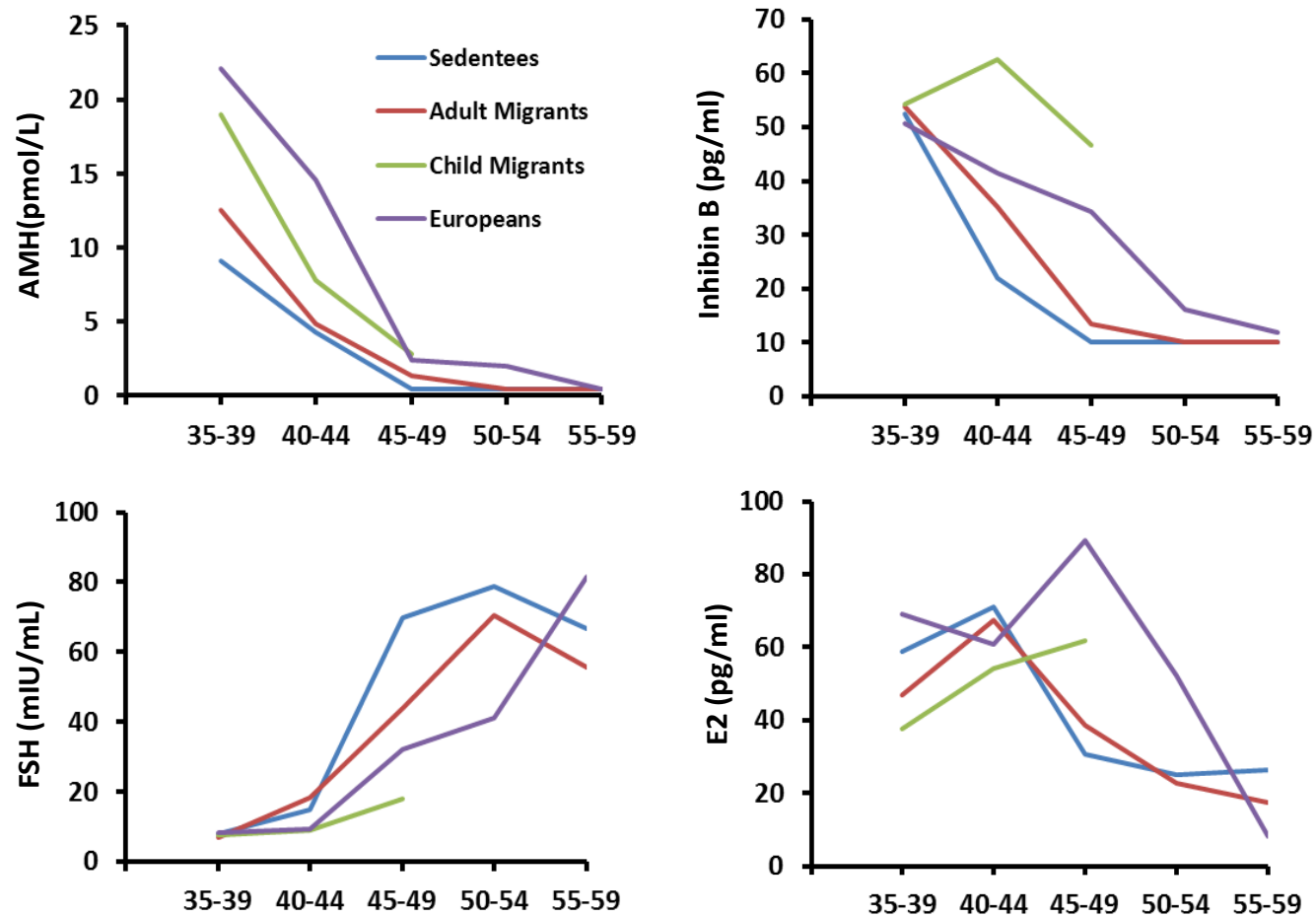


Figure 1

Supplementary Table 1 Mean (+ SEM) levels of serum reproductive hormones by age quintiles for Bangladeshi sedentees, migrants and European women.

	Sedentees	Adult Migrants	Child Migrants	Europeans
Age categories				
35-39 years				
Sample size (n)	8	14	21-24‡	9
Inhibin B (pg/ml)	52.54 ± 7.3	53.78 ± 11.1	54.29 ± 7.2	50.61 ± 10.7
AMH (pmol/L)	9.08 ± 2.44	12.55 ± 2.3	18.98 ± 3.1	22.07 ± 6.9
FSH (mIU/mL)	8.03 ± 1.26	7.17 ± 0.5	7.66 ± 0.5	8.5 ± 2.8
E2 (pg/ml)	58.86 ± 7.4	46.75 ± 3.9	37.72 ± 4.6	69.21 ± 31
40-44 years				
Sample size (n)	8	14	10	9
Inhibin B (pg/ml)	21.89 ± 6.0	35.21 ± 6.2	62.49 ± 9.7	41.46 ± 7.5
AMH (pmol/L)	4.27 ± 1.1	4.87 ± 1.5	7.8 ± 2.7	14.57 ± 4.4
FSH (mIU/mL)	14.94 ± 6.9	18.29 ± 4.5	9.2 ± 0.9	9.38 ± 1.7
E2 (pg/ml)	71.05 ± 12.1	67.51 ± 14.7	54.26 ± 10.8	60.8 ± 10.1
45-49 years				
Sample size (n)	4	10	5	13
Inhibin B (pg/ml)	10*	13.52 ± 2.35	46.55 ± 17.5	34.2 ± 7.8
AMH (pmol/L)	0.42*	1.38 ± 0.74	2.81 ± 0.8	2.44 ± 0.9
FSH (mIU/mL)	69.74 ± 30.57	44.0 ± 13.47	17.98 ± 8.9	32.25 ± 10.9
E2 (pg/ml)	30.57 ± 9.5	38.51 ± 15.6	61.67 ± 35.8	89.4 ± 21.4
50-54 years				
Sample size (n)	9	9	0†	8
Inhibin B (pg/ml)	10*	10*		16.02 ± 2.8
AMH (pmol/L)	0.45 ± 0.1	0.42*		2.0 ± 1.0
FSH (mIU/mL)	78.02 ± 17.37	70.53 ± 6.35		41.16 ± 14.2
E2 (pg/ml)	25.19 ± 4.7	22.64 ± 4.2		52.2 ± 22.2
54-59 years				
Sample size (n)	7	6	0†	11
Inhibin B (pg/ml)	10*	10*		11.78 ± 1.8
AMH (pmol/L)	0.42*	0.42*		0.43 ± 0
FSH (mIU/mL)	66.69 ± 7.79	55.67 ± 8.45		81.63 ± 6.5
E2 (pg/ml)	26.31 ± 3.5	17.3 ± 4.2		8.08 ± 0.9

*Below the limits of assay detectability for all women in this age quintile.

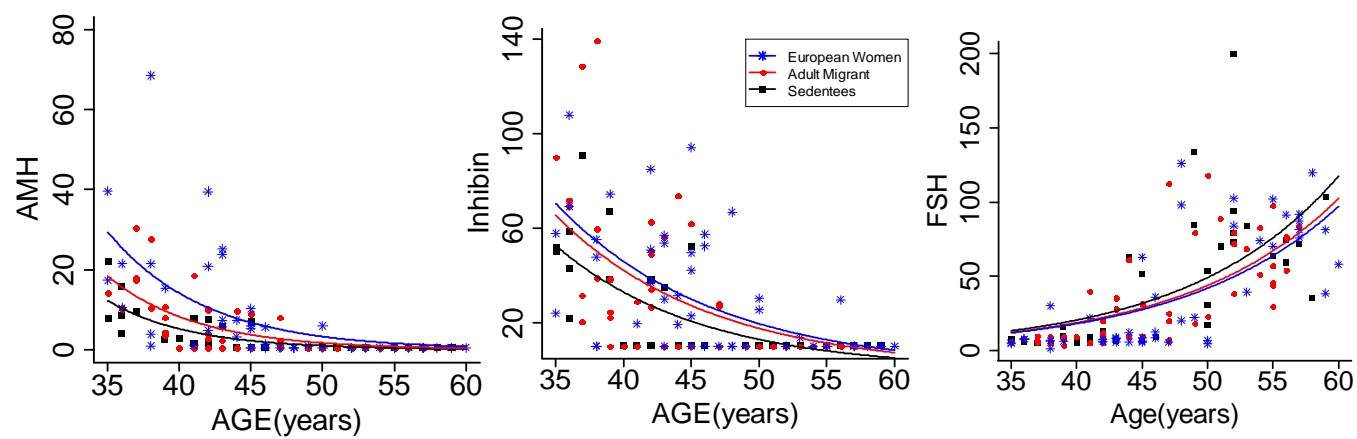
†Due to the history of Bangladeshi migration, no child migrants could be recruited into this group.

‡Sample size varies due to missing data in some cases.

Supplementary Table 2 Non-linear exponential model to estimate the age-related decline in AMH and inhibin and age-related increase in FSH.

	AMH			Inhibin			FSH		
Study groups*	Estimate	SE	P value	Estimate	SE	P value	Estimate	SE	P value
Sedentees	-0.172	0.021	<0.001	-0.094	0.012	<0.001	0.087	0.009	<0.001
Adult migrants	0.012	0.007	0.119	0.006	0.004	0.119	-0.002	0.003	0.362
European women	0.025	0.007	<0.001	0.008	0.004	0.036	-0.003	0.002	0.170

*child migrants are omitted due to the absence of subjects in the older age quintiles.



Supplementary Figure 1